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Photo Click Reaction of Acylsilanes with Indoles

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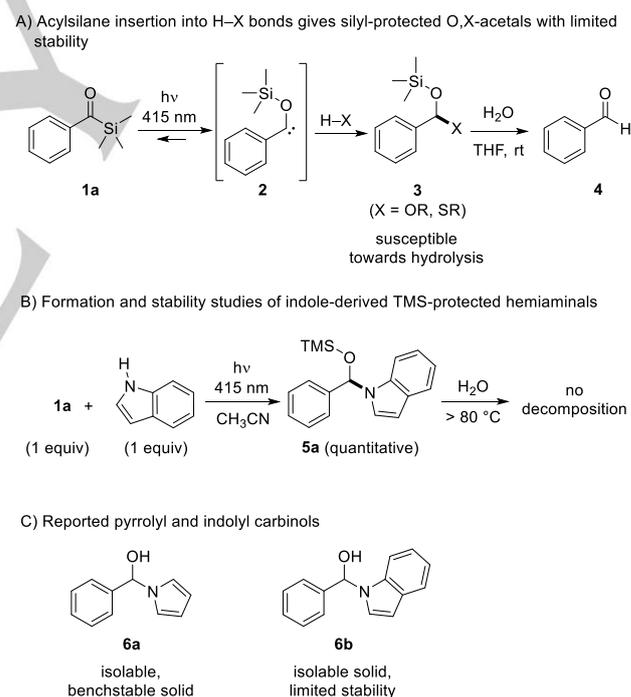
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Abstract: Light-mediated coupling of acylsilanes with indoles is reported. This photo click reaction occurs under mild conditions (415 nm) mostly in quantitative yield and provides stable silylated N,O-acetals via light mediated siloxycarbene generation with subsequent indole-N–H insertion. We show that this very efficient and fully atom economic coupling process can be applied to conjugate complex systems, as documented by the clicking of carbohydrates with indole alkaloids. The method is also applicable to the conjugation of polymer chains. The linking acetal moiety can be readily cleaved and it is also shown that wavelength-selective coupling and cleavage with acyl silanes bearing a second photoactive moiety is possible. This is documented by a successful polymerization/depolymerization sequence and by a polymer folding/unfolding process.

Photochemistry has recently gained great attention in synthetic chemistry and also in materials science, since light is cheap, allows for spatiotemporal control and can be tuned in terms of its wavelength and intensity, without producing any waste.^[1] These features render photochemistry highly valuable in synthesis and light-mediated processes have also found applications in biological chemistry.^[2] Considering materials science, systems bearing photoswitches^[3] and photocleavable functional groups^[4] have been designed. Moreover, light-mediated cycloaddition reactions^[5] or photopolymerizations^[6] have been applied to the construction of novel materials. As the irradiation wavelength can be easily varied, great efforts have been devoted to the development of wavelength-orthogonal processes,^[7] for example in the polymer field,^[8] in surface science,^[9] in supramolecular chemistry,^[10] and even in the context of photoredox catalysis.^[11]

Encouraged by our recent studies on the use of acylsilanes for light-mediated metal nanoparticle generation,^[12] we decided to apply such silanes as photolinkers for the mild conjugation (click reaction^[13]) of complex systems. Acylsilanes feature an elongated bond between the carbonyl group and the silyl moiety which is cleaved upon visible light irradiation (for acylsilanes with a π -system in conjugation to the carbonyl group).^[14] Thereby, a siloxycarbene is generated, a reactive intermediate whose utility in organic synthesis has been studied. Synthetic applications of acylsilanes include additions to carbon-carbon^[15] or carbon-oxygen^[16] multiple bonds as well as to alkyl boronates,^[17] among others.^[18] Insertion of *in situ* generated siloxycarbenes into hydrogen-heteroatom (H–X) bonds have also been reported.^[19] These H–X insertions usually occur with high efficiency. Regarding materials science, acylsilanes have only found limited applications, as light-responsive polymerisation initiators^[20] and for visible light

curing.^[21] The ability to generate reactive carbenes which can undergo fast insertion reactions with high selectivity by visible light irradiation, along with their ready access render acylsilanes promising candidates as reactive functionalities in materials chemistry. Moreover, light-mediated siloxycarbene generation from an acylsilane is a reversible process.^[22] The reversible nature of the silyl migration provides the reactive siloxycarbene a formal longer life-time as compared to the life-time of carbenes generated by other methods. This fact will be of high importance for X–H insertions in the area of materials science, where diffusion of the reaction partners may become the limiting factor. Herein we report our first results on the photo click reaction of acylsilanes with indoles.



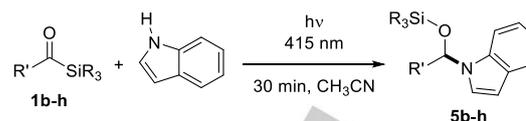
Scheme 1. A) Insertion of siloxycarbenes generated from acylsilanes into H–X bonds of alcohols and thiols provides unstable protected X,O-acetals. B) Indole-derived silylated N,O-acetals show higher stability, reminiscent of the stability of aminals **6**.

We first investigated the insertion of the carbene **2** generated from benzoylsilane **1a** upon 415 nm irradiation into H–X bonds of alcohols and thiols and found, in agreement with the literature^[19], efficient formation of the corresponding O-silyl-protected X,O-acetals **3** (Scheme 1 A). However, the insertion products **3** were susceptible towards hydrolysis to give

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benzaldehyde (**4**, see SI). Upon storage (neat) and also in solution in various solvents tested, decomposition of **3** was observed and therefore these acetal functionalities are not suitable as linking moieties in materials science. Motivated by the mostly quantitative X–H insertion reaction of **2** we were looking for reaction partners that lead to stable X,O-acetals and identified the indole moiety as an ideal functionality. Hence, blue light irradiation of a solution of an equimolar amount of acylsilane **1a** and indole in acetonitrile, THF or dichloromethane afforded quantitatively the insertion product **5a** (Scheme 1 B). In contrast to the X,O-acetals **3**, TMS-protected hemiaminal **5a** was bench stable for at least several weeks and stable in solution in various solvents (in benzene, in THF/D₂O at 60 °C, in wet acetonitrile at 80 °C). Slow decomposition was observed in acid-containing chloroform and in wet DMSO at 100 °C. The improved stability of **5a** can be explained by the lower leaving group ability of the indolide anion (pK_a = 21 in DMSO^[23]) as compared to the alcoholates and thiolates in its congeners **3**. Moreover, the indole N-atom in **5a** shows a low basicity leading to an increased acetal stability towards acid hydrolysis. Our findings are in line with the unusual high stability of pyrrolyl and indolyl carbinols **6a** and **6b** (Scheme 1 C).^[24] Besides the indole functionality, a few other RX–H coupling partners can be used although only the stability of amide-derived X,O-acetals can compete with that of acetal **5a** (see SI for detailed stability studies). Of note, attempted insertion of **2** into the N–H bond of aliphatic and aromatic amines failed, probably due to a competing dark reaction.^[25]

We then investigated the scope with respect to the acylsilane reagent in the reaction with indole (Scheme 2). Pleasingly, the photochemical insertion proceeded well when acylsilanes bearing electron rich (**1b**), electron deficient (**1c**) or sterically demanding (**1d**) aryl moieties were employed and acetals **5b–5d** were obtained in quantitative yields. With the aliphatic acylsilane **1e**, the insertion product **5e** was formed in 64% yield, which was increased to 76% for insertion product **5f** bearing a triethylsilyl group. When employing the corresponding acylsilane with a bulky diphenyl(*tert*-butyl)silyl group, the corresponding insertion product could not be separated from side products although crude NMR and high resolution mass spectrometry confirmed the formation of the acetal. Interestingly, the X–H insertion product is formed in quantitative yield when phenol is used as coupling partner for aliphatic acylsilanes (see SI). Benzoylsilanes **1g** and **1h** bearing larger silyl substituents also engage in the reaction with indole. For the triethylsilyl derivative, N–H-insertion proceeded quantitatively (**5g**, 99%), whereas a slightly reduced yield was noted for the triisopropyl congener (**5h**, 90%).

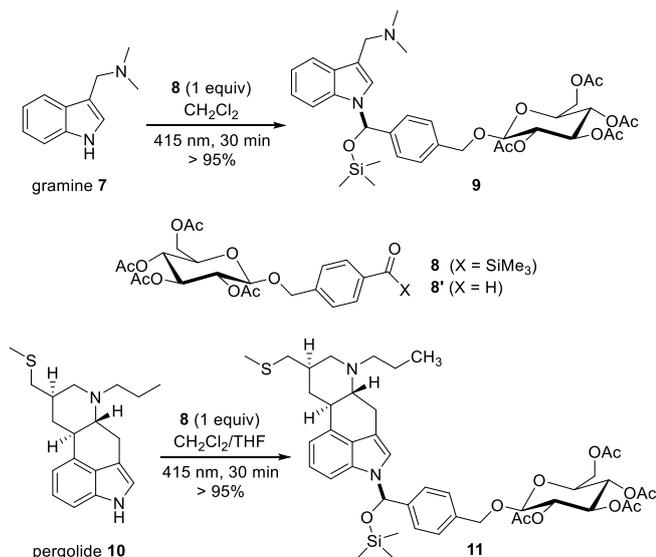


1b (R = Me, R' = p-MeO-C ₆ H ₄)	5b (99%, R = Me, R' = p-MeO-C ₆ H ₄)
1c (R = Me, R' = p-CF ₃ -C ₆ H ₄)	5c (99%, R = Me, R' = p-CF ₃ -C ₆ H ₄)
1d (R = Me, R' = o-CH ₃ -C ₆ H ₄)	5d (99%, R = Me, R' = o-CH ₃ -C ₆ H ₄)
1e (R = Me, R' = Me)	5e (64%, ^[a] R = Me, R' = Me)
1f (R = Me, R' = Et)	5f (76%, ^[a] R = Me, R' = Et)
1g (R = Et, R' = Ph)	5g (99%, R = Et, R' = Ph)
1h (R = <i>i</i> -Pr, R' = Ph)	5h (90%, ^[b] R = <i>i</i> -Pr, R' = Ph)

Scheme 2. Variation of the acylsilane. Reaction conditions: acylsilane (0.1 mmol, 1.0 equiv), indole (0.1 mmol, 1.0 equiv.), CH₃CN (2 mL), three 3 W 415 nm LED's, room temperature. [a] Irradiation for 7.5 h in MeCN (0.5 mL). [b] Irradiation for 60 min until full consumption of **1h**.

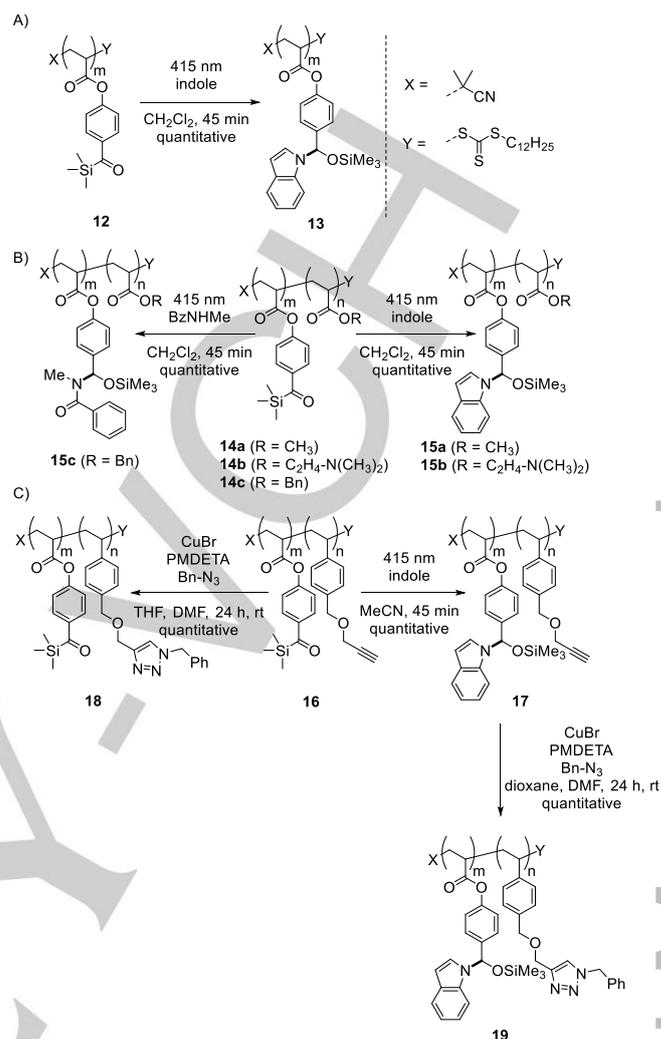
If required, the N,O-acetal of type **5** can be readily converted under mild conditions to the corresponding aldehyde and indole. For example, treatment of **5a** with CsF in acetonitrile provided quantitatively benzaldehyde and indole. Thus, the indole moiety can be protected and deprotected under mild conditions in excellent yields in both directions. To document the potential of this novel conjugation method, the indole N–H insertion was applied to more complex systems. The indole core is ubiquitous in organic chemistry and is found in various alkaloids and also in drugs, making such compounds viable targets for our method. Along these lines, we decided to apply the N–H insertion to the conjugation of indole alkaloids with the β-D-glucose derivative **8** (for the synthesis of **8**, see SI) and chose gramine (**7**), which is a simple natural product occurring in maple and barley,^[26] as a first substrate. Pleasingly, 415 nm light irradiation of a solution of equimolar amounts of **8** and gramine (**7**) gave the TMS-protected hemiaminal **9** in >95% yield as a 1:1 mixture of diastereoisomers (Scheme 3). Reaction of **8** with the more complex alkaloid pergolide (**10**), a well-known dopamine agonist which is dispensed to patients with Parkinson's disease^[27], under similar conditions worked equally well and the targeted conjugate **11** was formed in excellent yield. Deconjugation was documented on **9** by treatment with CsF in acetonitrile to give the glucose derivative **8'** in 96% yield along with gramine (**7**, 86%). The slightly reduced yield of recovered **7** was due to product loss during isolation.

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Scheme 3. Light-induced coupling of glucose derivative **8** with indole alkaloids.

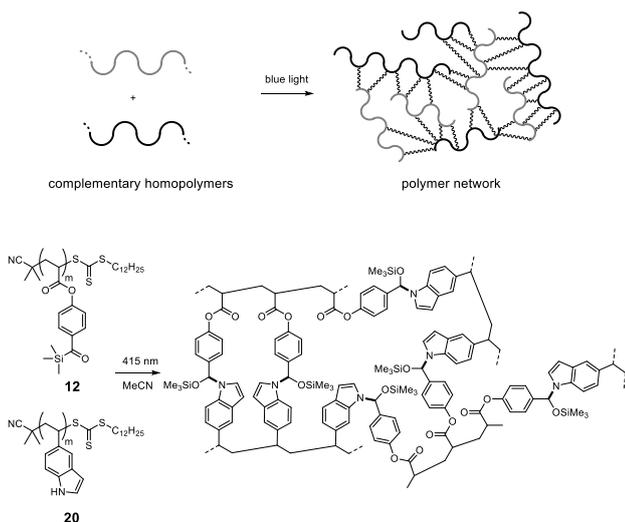
Having established that the light-mediated coupling works efficiently on low molecular weight compounds, we further applied the conjugation method to polymers. To this end, various polymeric acylsilanes were prepared by living radical polymerization (RAFT, see SI). Irradiation of the high molecular weight homopolymer **12** ($M_n \approx 23.5 \text{ kg mol}^{-1}$) in dry CH₂Cl₂ in the presence of indole provided the poly-acetal **13** ($M_n \approx 24.7 \text{ kg mol}^{-1}$, Scheme 4 A). Based on NMR analysis, a quantitative transformation of the acylsilane moieties into the corresponding acetal functionalities was achieved.^[28] Moreover, the method could be applied to the functionalization of statistical copolymers. The methyl acrylate containing copolymer **14a** ($M_n \approx 7.3 \text{ kg mol}^{-1}$) and the copolymer **14b** ($M_n \approx 4.8 \text{ kg mol}^{-1}$) bearing basic tertiary amino groups in their side chains were both capped with indole quantitatively (**15a**, **15b**, Scheme 4 B). We also found quantitative coupling with an amide functionality by capping the benzyl acrylate containing copolymer **14c** ($M_n \approx 20.1 \text{ kg mol}^{-1}$) with *N*-methylbenzamide to give polymer **15c**. Moreover, the method was also applied to chemically modify the copolymer **16** ($M_n \approx 11.8 \text{ kg mol}^{-1}$) containing additionally orthogonally addressable C≡C triple bonds. Thus, 415 nm irradiation of **16** in the presence of indole led to chemoselective functionalization of the acylsilyl side chains (**17**, Scheme 4 C). Alternatively, the alkyne side chains could be functionalized selectively via cycloaddition with benzyl azide using CuBr/pentamethyldiethylenetriamine (PMDETA) as catalyst system to give the polymeric triazole **18**. Importantly, the acylsilane moiety remained unreacted and based on proton NMR analysis, both orthogonal transformations occurred in quantitative yields. Moreover, iterative double functionalization of copolymer **16** was achieved by applying both click reactions subsequently. This was documented by performing the cycloaddition reaction on polymer **17** to give **19**, again in quantitative yield based on proton NMR analysis. Due to poor solubility of functionalized copolymer **18**, applying our photo-click reaction to form doubly functionalized polymer **19** via the alternative route was not implemented.



Scheme 4. Indole/acylsilane conjugation in polymeric systems.

Next, we applied the click reaction to light-induced polymer network formation. A concentrated solution of polymeric acylsilane **12** ($M_n \approx 23.5 \text{ kg mol}^{-1}$) and poly 5-vinylindole **20** ($M_n \approx 1.7 \text{ kg mol}^{-1}$) in acetonitrile was charged onto a rheometer and irradiated with a blue LED (Scheme 5). The reaction progress was monitored by measuring the changes in viscosity η during continuous shearing of the sample (Figure 1). As expected, a strong increase in the viscosity was observed, after irradiation for 120 seconds. After 10 min, the sample solidified.

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Scheme 5. Polymer network formation via light-mediated crosslinking of polymeric acylsilane **12** and polyindole **20**.

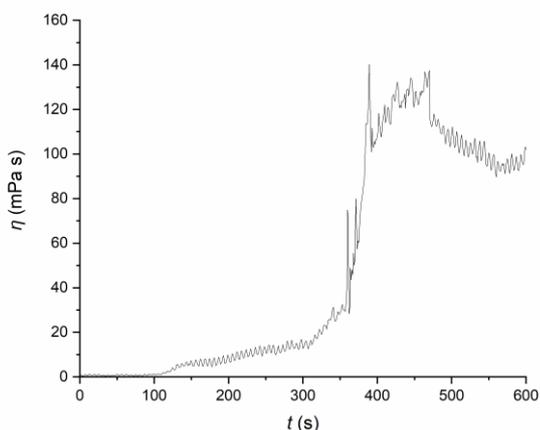
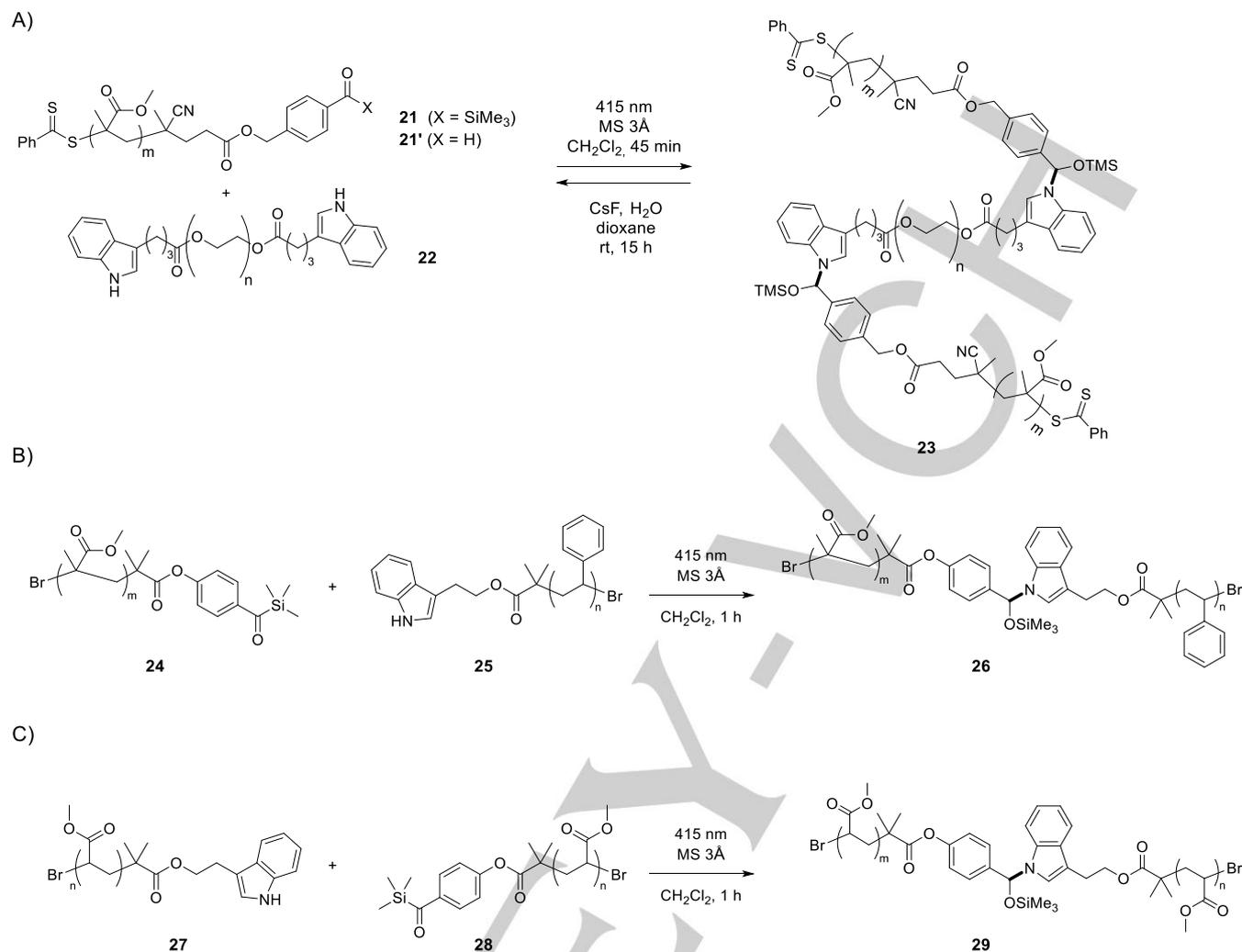


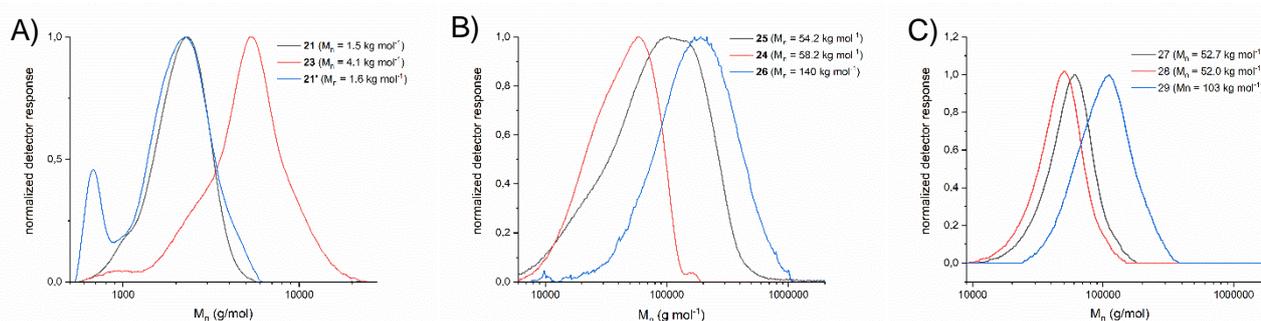
Figure 1. Polymer network formation monitored via changes in viscosity of the reaction solution.

In addition to side chain functionalization, the method can also be applied to block copolymer synthesis by reacting polymers containing single indole or acylsilyl moieties at the terminus. Poly(methyl methacrylate) **21** ($M_n \approx 1.5 \text{ kg mol}^{-1}$) bearing an acyl silane entity at the terminus was successfully conjugated with the bis-indolyl-polyethylene glycol (PEG) **22** ($M_n \approx 1.4 \text{ kg mol}^{-1}$) to provide the ABA triblock copolymer **23** (Scheme 6 A). The successful conjugation of the two short polymers was confirmed by NMR spectroscopy (see SI) and GPC analysis (Figure 2). Furthermore, we demonstrated cleavage of the triblock copolymer **23** by treatment with CsF in THF/water to reform **22** along with the poly(methyl methacrylate) **21'**. The ligation method is also applicable to link high molecular weight polymers. Hence, acylsilyl-terminated poly(methyl methacrylate) **24** ($M_n \approx 58.2 \text{ kg mol}^{-1}$) and indole-terminated polystyrene **25** ($M_n \approx 54.2 \text{ kg mol}^{-1}$) were efficiently coupled to give the diblock copolymer **26** (Scheme 6 B). In addition, we demonstrated quantitative coupling of two narrow dispersity polymethylacrylates terminated with an indole (**27**, $M_n = 52.7 \text{ kg mol}^{-1}$) and with an acylsilyl group (**28**, $M_n = 52.0 \text{ kg mol}^{-1}$) to give polymer **29** ($M_n = 103 \text{ kg mol}^{-1}$, Scheme 6C).

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Scheme 6. Block copolymer synthesis.

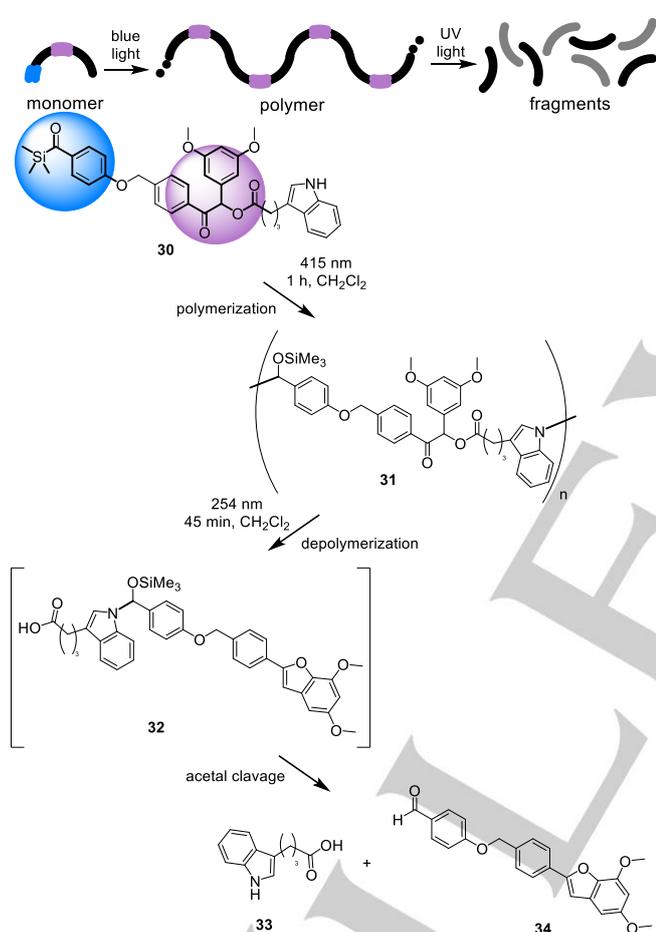
Figure 2. GPC traces of A) polymer **21** (black), triblock copolymer **23** (red) and cleaved polymer **21'** (blue), B) poly(methyl methacrylate) **24** (red), polystyrene **25** (black) and block copolymer **26** (blue), C) polymer **27** (black), **28** (red), **29** (blue).

Next, we aimed for the application of the method to λ -orthogonal systems which can engage in wavelength-controlled processes. Acylsilane **30** (see SI) bearing an additional orthogonally UV-photoaddressable α -alkoxy ketone moiety and the indole functionality was designed. This monomer should allow for a wavelength-controlled polymerization and depolymerization sequence using light as the only “reagent”, as sketched at the top

of Scheme 7. Polymerization was conducted upon 415 nm irradiation of **30** via multiple siloxycarbene/N-H insertions to give polyaminal **31**, as analyzed using GPC and NMR methods. The polymers obtained were terminated by an aldehyde moiety which was formed by reaction of the siloxycarbene intermediate with trace amounts of water. Integration of the aldehyde proton against the benzylic CH₂ protons showed a ratio of 1:44, which allows to

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estimate an average chain length of 22 monomers for **31** ($M_n \approx 14.6 \text{ kg mol}^{-1}$). Surprisingly, this is in good agreement with the polymer's GPC data revealing a M_n of around 13.8 kg mol^{-1} using poly(methyl methacrylate) as the standard. The polymer was also investigated by differential scanning calorimetry (DSC) which allowed to determine its glass transition as $T_g = 55 \text{ }^\circ\text{C}$. Depolymerization could be achieved by UV-light irradiation (254 nm) of **31** to provide carboxylic acid **32**. The UV-induced cleavage of such an α -alkoxy ketone moiety to give a benzofuran and a carboxylic acid functionality is an established photoreaction.^[29] However, the N,O-acetal moiety of compound **32** that also contains an acid functionality was found to be unstable under the reaction conditions and acid-induced acetal cleavage eventually provided the fragments **33** and **34** as the final products, as confirmed by NMR analysis (see SI).

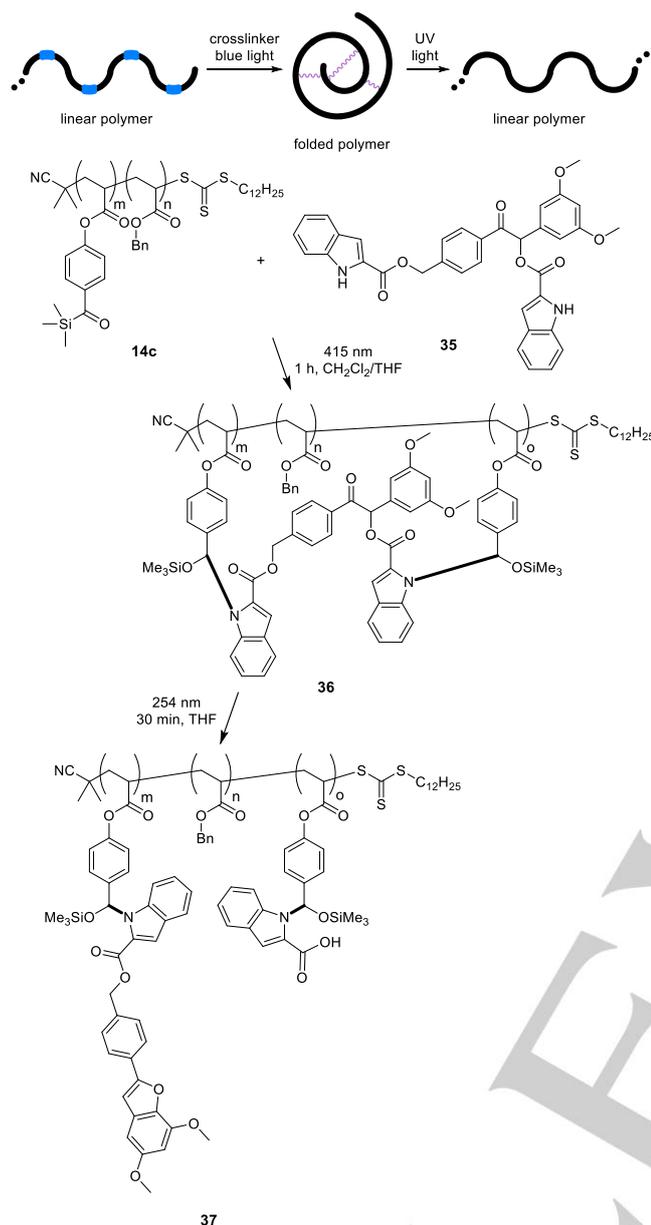


Scheme 7. Wavelength-controlled crosslinking and crosslinker cleavage in single polymer chains.

Finally, we could show that such λ -orthogonal photochemistry can be used to control intramolecular crosslinking and crosslinker cleavage in polymer chains, as depicted in Scheme 8. To this end, linear copolymer **14c** was prepared by living radical polymerization of benzyl acrylate and acylsilane monomers. Irradiation of a dilute solution of polymer **14c** in the presence of photocleavable crosslinker **35** ($c(\mathbf{35}) \approx 1.8 \cdot 10^{-4} \text{ M}$) with blue light led to folding of single polymer strands by multiple intramolecular crosslinking events (see **36**).^[30] Thereby, single chain polymer

nanoparticles **36** were formed, showing globular shape as compared to the linear precursor polymer **14c**. The altered shape of the nanoparticles led to longer retention times in GPC analysis (Figure 3), which is characteristic for folded polymers with increased compactness. Notably, this effect outcompetes the significant gain in the polymer's actual molecular weight due to incorporation of the crosslinkers. The nanoparticle can be retransformed into linear polymer chains by UV-light mediated cleavage of the α -alkoxy ketone crosslinkers. Hence, 254 nm irradiation of a solution of cross-linked polymer **36** in THF gave the polymer **37** bearing N,O-acetal functionalities at their side chains. As expected, this unfolding process to yield linear polymer chains caused a decrease in retention time of the GPC trace (Figure 3, blue line).^[31] Since the observed changes in retention time were minimal, as it is always the case when single chain collapse is monitored, we mimicked and reproduced this process by using resorcinol as a commercial crosslinker (see SI). Again, light-mediated single chain collapse led to smaller apparent molecular weights, as determined by GPC. Cleavage of the crosslinkers was achieved by acidic hydrolysis, again causing a shift of the GPC traces towards higher molecular weights.

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Scheme 8. Wavelength-controlled folding and unfolding of a linear polymer.

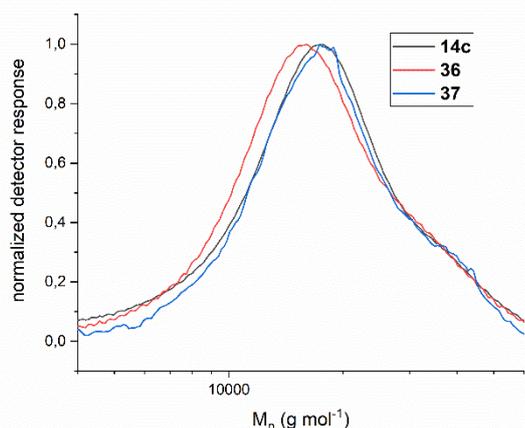


Figure 3. Single chain crosslinking and crosslinker cleavage monitored by GPC.

In summary, we have introduced the visible light-mediated coupling between acylsilanes and indole derivatives as a valuable photoclick reaction for conjugation of small molecules and macromolecules. The mild photoreaction is highly efficient, fast and selective, giving rise to robust and thermally stable N,O-acetal connections which do not hydrolyse in neutral media in various solvents. The method's applicability to a variety of systems has been documented by quantitative coupling of a sugar derivative to two indole alkaloids and by the conjugation, crosslinking and folding of polymers. Importantly, the silyloxy acetal moiety can be readily cleaved under mild conditions, rendering acylsilanes promising novel indole N-protecting groups. Notably, photochemical X-H insertion leading to stable products also works on amides and phenols as the coupling partners of the acyl silanes. Moreover, we have shown that a combination of acylsilane and an additional UV-cleavable moiety can be used for wavelength-selective polymerization/depolymerization with light as the only "reagent". We are confident that the herein introduced acylsilane/indole photo click reaction will find many applications in organic synthesis and also in the field of materials science.

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Conflict of Interest

There is no conflict of interest.

Keywords: Acylsilanes • Indoles • Click-Chemistry • Polymers • Photochemistry

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RESEARCH ARTICLE

Entry for the Table of Contents

C. Stuckhardt, M. Wissing, A. Studer

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Photo Click Reaction of Acylsilanes with Indoles

Photo Click. Visible light-mediated coupling of acylsilanes with indoles is reported. This photoreaction occurs under mild conditions mostly in quantitative yield and provides stable silylated N,O-acetals. The potential of the method is documented by the successful coupling of carbohydrates with indole alkaloids and by the conjugation of polymers.

